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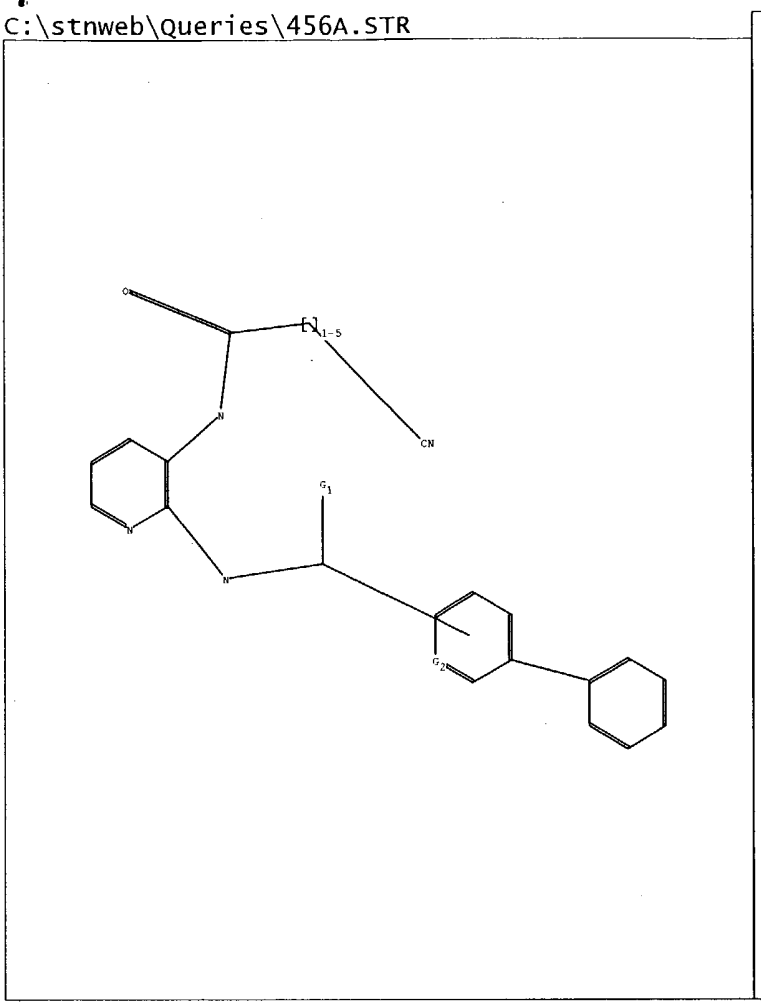


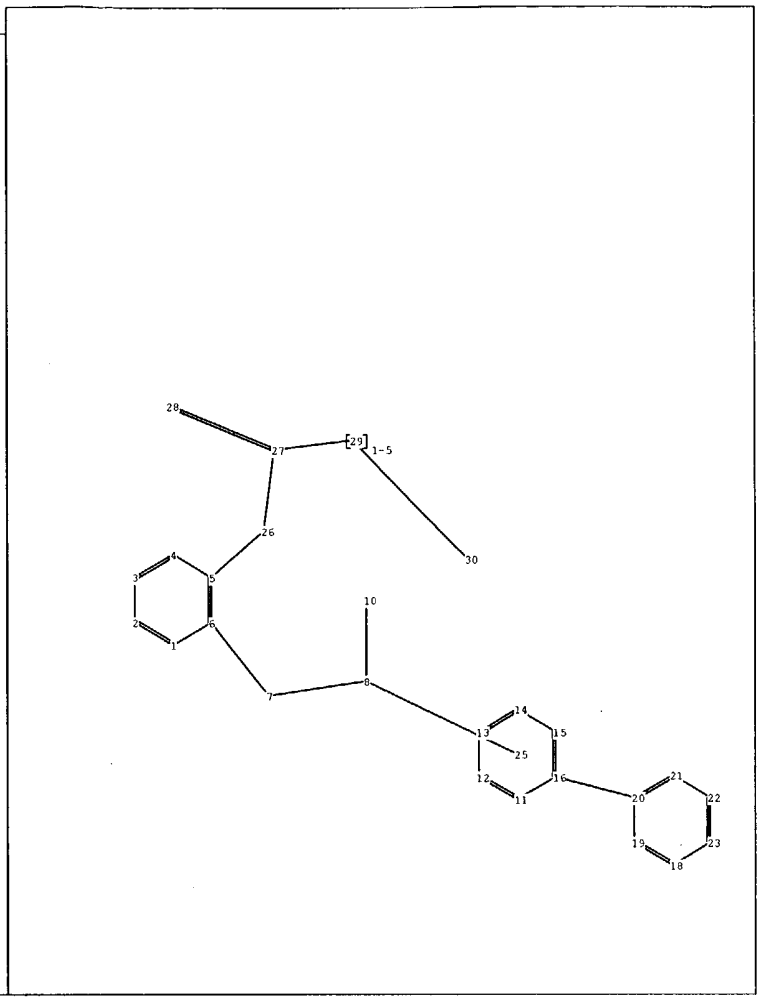


chain nodes :
7 8 10 26 27 28 29 30
ring nodes :
1 2 3 4 5 6 11 12 13 14 15 16 18 19 20 21 22 23
chain bonds :
5-26 6-7 7-8 8-10 16-20 26-27 27-28 27-29 29-30
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 11-12 11-16 12-13 13-14 14-15 15-16 18-19 18-23
19-20 20-21 21-22 22-23
exact/norm bonds :
5-26 6-7 7-8 8-10 11-12 11-16 12-13 13-14 14-15 15-16 16-20 26-27 27-28
27-29 29-30
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 18-19 18-23 19-20 20-21 21-22 22-23
isolated ring systems :
containing 1 : 11 : 18 :

G1:H,Ak

G2:N,CH

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:CLASS 10:CLASS 11:Atom
12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 18:Atom 19:Atom 20:Atom 21:Atom 22:Atom
23:Atom 25:CLASS 26:CLASS 27:CLASS 28:CLASS 29:CLASS 30:CLASS

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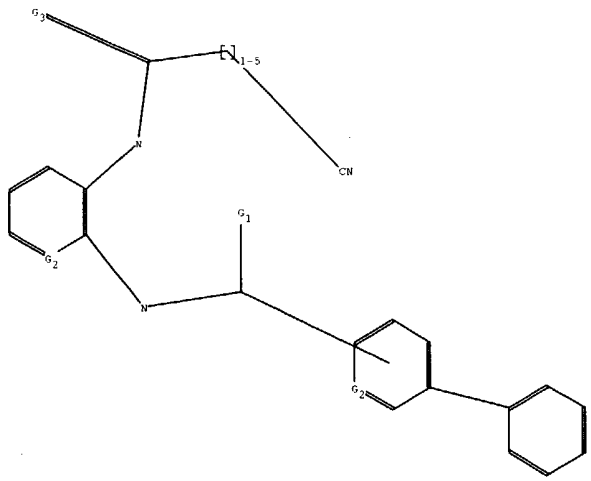


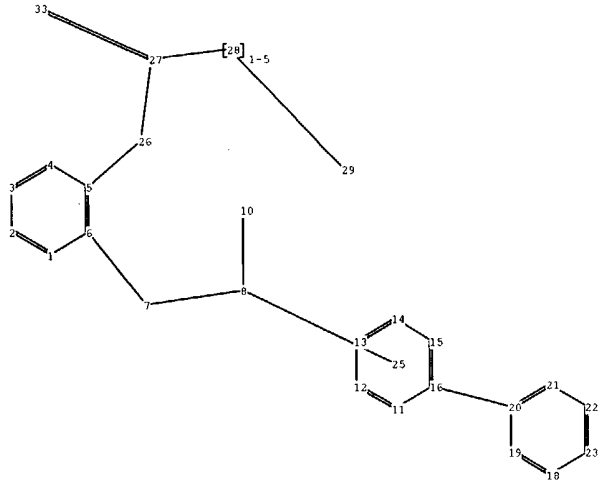


chain nodes :
7 8 10 26 27 28 29 33
ring nodes :
1 2 3 4 5 6 11 12 13 14 15 16 18 19 20 21 22 23
chain bonds :
5-26 6-7 7-8 8-10 16-20 26-27 27-28 27-33 28-29
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 11-12 11-16 12-13 13-14 14-15 15-16 18-19 18-23
19-20 20-21 21-22 22-23
exact/norm bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-26 6-7 7-8 8-10 11-12 11-16 12-13 13-14 14-15
15-16 16-20 26-27 27-28 27-33 28-29
normalized bonds :
18-19 18-23 19-20 20-21 21-22 22-23
isolated ring systems :
containing 1 : 11 : 18 :

G1:H,Ak,OH,NH2,F

G2:N,CH

G3:O,S

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:CLASS 10:CLASS 11:Atom
12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 18:Atom 19:Atom 20:Atom 21:Atom 22:Atom
23:Atom 25:CLASS 26:CLASS 27:CLASS 28:CLASS 29:CLASS 33:CLASS

```
* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2           "Ask CAS" for self-help around the clock
 NEWS  3  JAN 27   Source of Registration (SR) information in REGISTRY updated
                   and searchable
 NEWS  4  JAN 27   A new search aid, the Company Name Thesaurus, available in
                   CA/CAplus
 NEWS  5  FEB 05   German (DE) application and patent publication number format
                   changes
 NEWS  6  MAR 03   MEDLINE and LMEDLINE reloaded
 NEWS  7  MAR 03   MEDLINE file segment of TOXCENTER reloaded
 NEWS  8  MAR 03   FRANCEPAT now available on STN
 NEWS  9  MAR 29   Pharmaceutical Substances (PS) now available on STN
 NEWS 10  MAR 29   WPIFV now available on STN
 NEWS 11  MAR 29   New monthly current-awareness alert (SDI) frequency in RAPRA
 NEWS 12  APR 26   PROMT: New display field available
 NEWS 13  APR 26   IFIPAT/IFIUDB/IFICDB: New super search and display field
                   available
 NEWS 14  APR 26   LITALERT now available on STN
 NEWS 15  APR 27   NLDB: New search and display fields available
 NEWS 16  May 10   PROUSDDR now available on STN
 NEWS 17  May 19   PROUSDDR: One FREE connect hour, per account, in both May
                   and June 2004
 NEWS 18  May 12   EXTEND option available in structure searching
 NEWS 19  May 12   Polymer links for the POLYLINK command completed in REGISTRY
 NEWS 20  May 17   FRFULL now available on STN
 NEWS 21  May 27   STN User Update to be held June 7 and June 8 at the SLA 2004
                   Conference
 NEWS 22  May 27   New UPM (Update Code Maximum) field for more efficient patent
                   SDIs in CAplus
 NEWS 23  May 27   CAplus super roles and document types searchable in REGISTRY
 NEWS 24  May 27   Explore APOLLIT with free connect time in June 2004

 NEWS EXPRESS  MARCH 31 CURRENT WINDOWS VERSION IS V7.00A, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 26 APRIL 2004
 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
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FILE 'HOME' ENTERED AT 17:22:43 ON 06 JUN 2004

=> file reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21
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FILE 'REGISTRY' ENTERED AT 17:23:01 ON 06 JUN 2004
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STRUCTURE FILE UPDATES: 4 JUN 2004 HIGHEST RN 689739-78-4
DICTIONARY FILE UPDATES: 4 JUN 2004 HIGHEST RN 689739-78-4

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

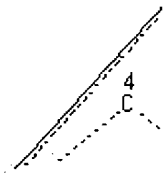
Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=>
L1 STRUCTURE UPLOADED

=> D L1
L1 HAS NO ANSWERS
L1 STR

N 32 C M1

H 29 Ak 30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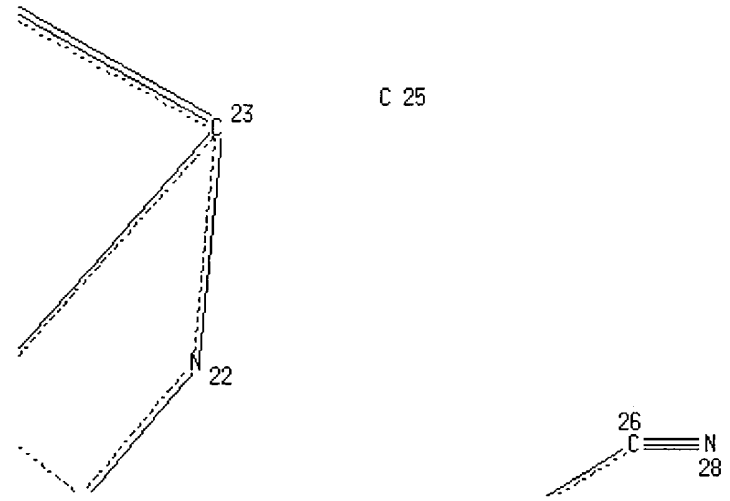


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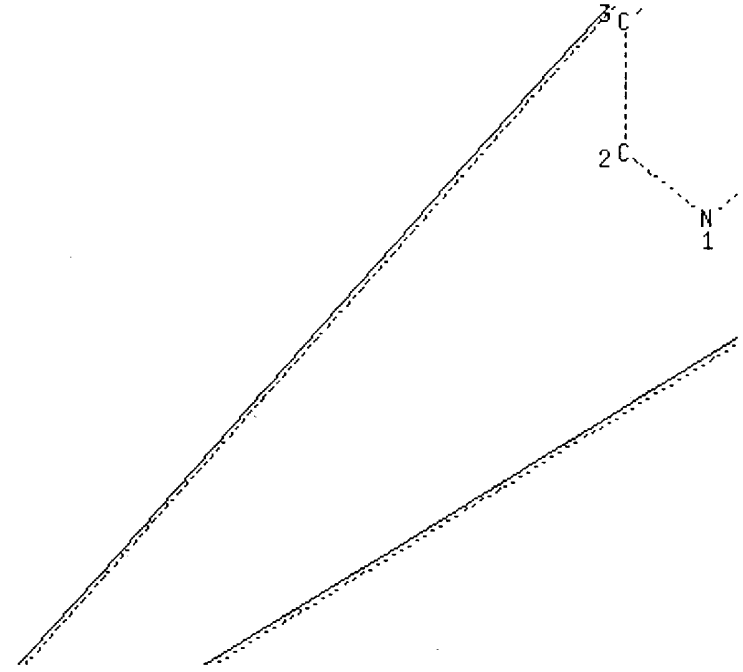
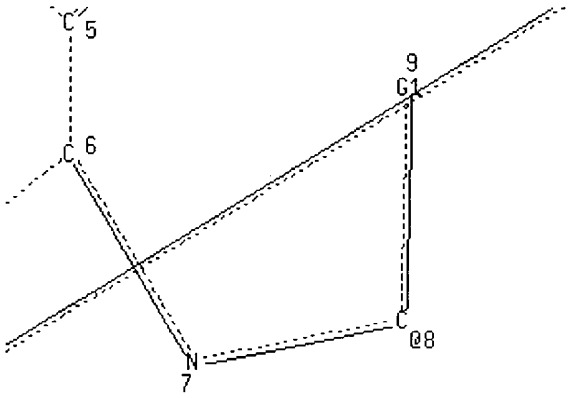
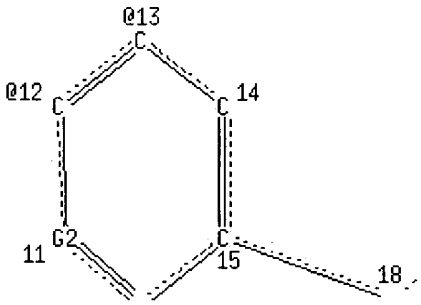



Page 2-A

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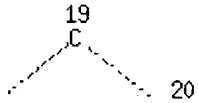
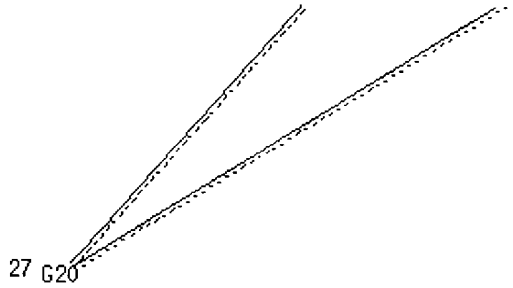
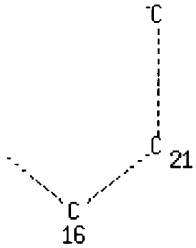



Page 2-C




Page 3-A


Page 3-B




Page 3-C
VAR G1=29/30
VAR G2=31/32

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REP G20=(1-5) 25-23 25-26
VPA 8-12/13 S
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NSPEC   IS R      AT   1
NSPEC   IS R      AT   2
NSPEC   IS R      AT   3
NSPEC   IS R      AT   4
NSPEC   IS R      AT   5
NSPEC   IS R      AT   6
NSPEC   IS C      AT   7
NSPEC   IS C      AT   8
NSPEC   IS C      AT   9
NSPEC   IS R      AT  10
NSPEC   IS R      AT  11
NSPEC   IS R      AT  12
NSPEC   IS R      AT  13
NSPEC   IS R      AT  14
NSPEC   IS R      AT  15
NSPEC   IS R      AT  16
NSPEC   IS R      AT  17
NSPEC   IS R      AT  18
NSPEC   IS R      AT  19
NSPEC   IS R      AT  20
NSPEC   IS R      AT  21
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NSPEC   IS C      AT  23
NSPEC   IS C      AT  24
NSPEC   IS C      AT  25
NSPEC   IS C      AT  26
NSPEC   IS C      AT  27
NSPEC   IS C      AT  28
DEFAULT MLEVEL IS ATOM
MLEVEL  IS CLASS  AT   7  8 22 23 24 25 26 28 29 30
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS  32

STEREO ATTRIBUTES: NONE


=> s l1
SAMPLE SEARCH INITIATED 17:30:38 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -      7 TO ITERATE

100.0% PROCESSED       7 ITERATIONS                          6 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            7 TO      298
PROJECTED ANSWERS:               6 TO      266

L2            6 SEA SSS SAM L1

=> s l1 full
THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 155.00 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
```

```
FULL SEARCH INITIATED 17:30:43 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -    210 TO ITERATE

100.0% PROCESSED     210 ITERATIONS                          188 ANSWERS
SEARCH TIME: 00.00.01

L3          188 SEA SSS FUL L1

=> file hcaplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   160.46     160.67

FILE 'HCAPLUS' ENTERED AT 17:30:46 ON 06 JUN 2004
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FILE COVERS 1907 - 6 Jun 2004  VOL 140 ISS 24
FILE LAST UPDATED: 4 Jun 2004  (20040604/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


=> s l3
L4            1 L3

=> d l4, ibib abs fhitstr, 1

L4   ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2004 ACS on STN
```

Full Text | Citing References

```
ACCESSION NUMBER:         2004:182533  HCAPLUS
DOCUMENT NUMBER:          140:235608
TITLE:                    Preparation of 2-(biarylalkyl)amino-3-
                          (cyanoalkanoylamino)pyridines as bradykinin B1
                          antagonists for treating pain and inflammation
INVENTOR(S):              Kuduk, Scott D.; Bock, Mark G.; Feng, Dong-mei; Su,
                          Dai-shi; Wai, Jenny Miu-chun
PATENT ASSIGNEE(S):       USA
SOURCE:                   U.S. Pat. Appl. Publ., 28 pp.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.       KIND  DATE           APPLICATION NO.  DATE
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| | | | | | |
|---|---|---|---|---|---|
| US 2004044041 | A1 | 20040304 | US 2003-634426 | | 20030805 |
| PRIORITY APPLN. INFO.: | | | US 2002-401386P | P | 20020806 |

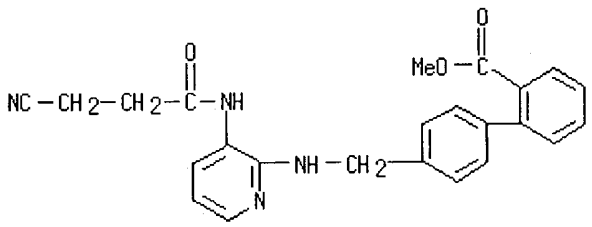
OTHER SOURCE(S): MARPAT 140:235608
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compds. [I; m = 1-4; X, Y = CH, or one is CH and the other is N; R1, R2 = H, alkyl; R3 = H, alkyl, haloalkyl, etc.; R4 = H, NO2, halo, etc.; R51, R52 = H, Me; or R51 and R52 together complete cycloalkyl ring; R61 = (un)substituted alkyl, cycloalkyl, alkenyl, etc.; R62, R63 = H, R61; with the proviso that not more than one of R61, R62 and R63 = heterocycle; R7 = H, alkyl, cycloalkyl, aryl, arylalkyl] which are bradykinin B1 antagonist compds. useful in the treatment or prevention of symptoms such as pain and inflammation assocd. with the bradykinin B1 pathway, were prepd. and formulated. E.g., a multi-step synthesis of II (starting from 4'-methyl-2-biphenylcarboxylic acid), was given. The compds. I have affinity for B1 receptor with IC50 values of < 5 μM.

IT **668472-10-4P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 2-(biarylalkyl)amino-3-(cyanoalkanoylamino)pyridines as bradykinin B1 antagonists)

RN 668472-10-4 HCAPLUS
CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[[[3-[(3-cyano-1-oxopropyl)amino]-2-pyridinyl]amino]methyl]-, methyl ester (9CI) (CA INDEX NAME)




=> file caold

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 7.12 | 167.79 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| CA SUBSCRIBER PRICE | -0.69 | -0.69 |

FILE 'CAOLD' ENTERED AT 17:31:21 ON 06 JUN 2004
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FILE COVERS 1907-1966
FILE LAST UPDATED: 01 May 1997 (19970501/UP)

```
  This file contains CAS Registry Numbers for easy and accurate
  substance identification.  Title keywords, authors, patent
  assignees, and patent information, e.g., patent numbers, are
  now searchable from 1907-1966.  TIFF images of CA abstracts
  printed between 1907-1966 are available in the PAGE
  display formats.

  This file supports REG1stRY for direct browsing and searching of
  all substance data from the REGISTRY file.  Enter HELP FIRST for
  more information.

=> d his

     (FILE 'HOME' ENTERED AT 17:22:43 ON 06 JUN 2004)

     FILE 'REGISTRY' ENTERED AT 17:23:01 ON 06 JUN 2004
L1              STRUCTURE UPLOADED
L2            6 S L1
L3          188 S L1 FULL

     FILE 'HCAPLUS' ENTERED AT 17:30:46 ON 06 JUN 2004
L4            1 S L3

     FILE 'CAOLD' ENTERED AT 17:31:21 ON 06 JUN 2004

=> s l3
L5            0 L3

=> file reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.42     168.21

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                         ENTRY    SESSION
CA SUBSCRIBER PRICE                                       0.00      -0.69

FILE 'REGISTRY' ENTERED AT 17:31:26 ON 06 JUN 2004
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STRUCTURE FILE UPDATES:    4 JUN 2004  HIGHEST RN 689739-78-4
DICTIONARY FILE UPDATES:   4 JUN 2004  HIGHEST RN 689739-78-4

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

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Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html
```

```
=>
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L6 HAS NO ANSWERS
L6                 STR
 O 36 S 37

 N 35 C M1

 H 29 Ak3300 B2 N M2 F 33
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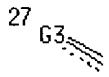


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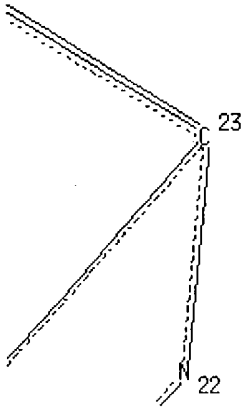
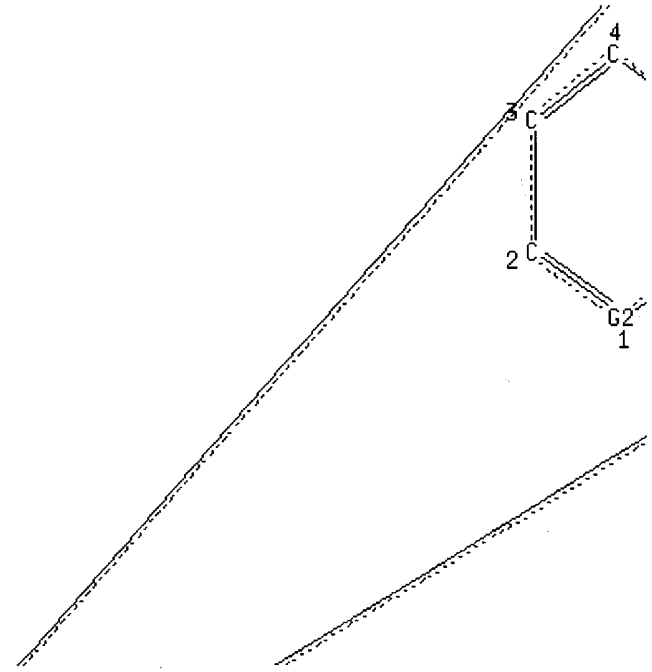
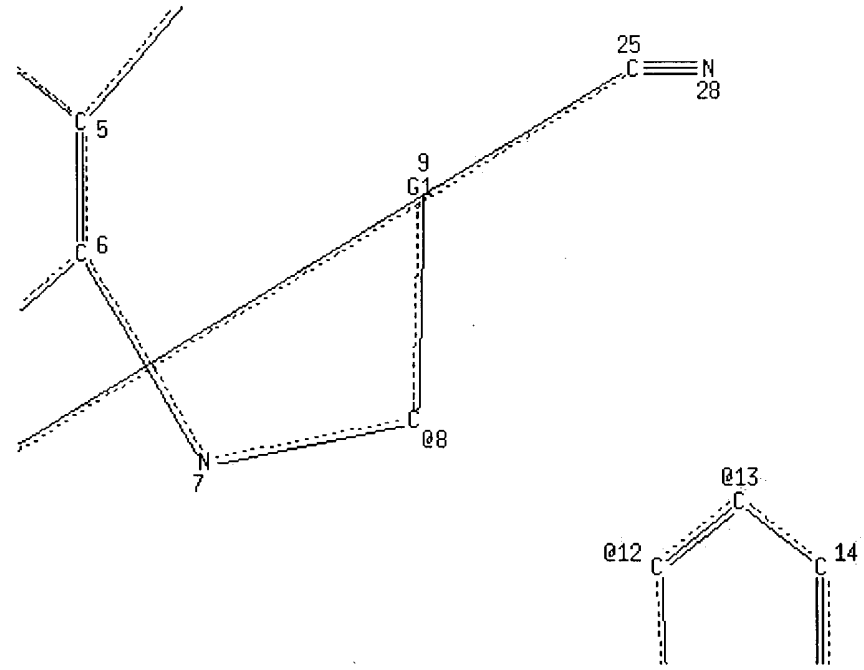


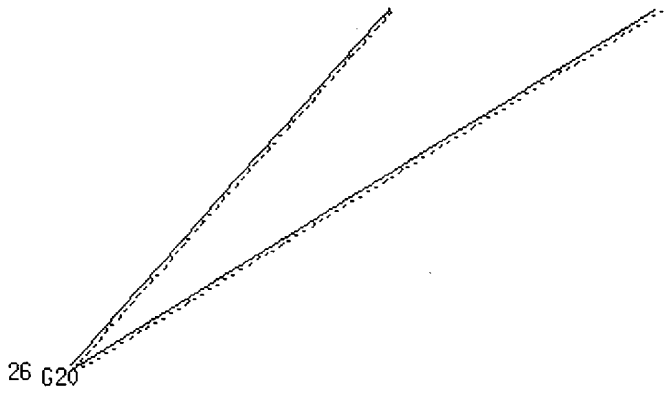

Page 1-B



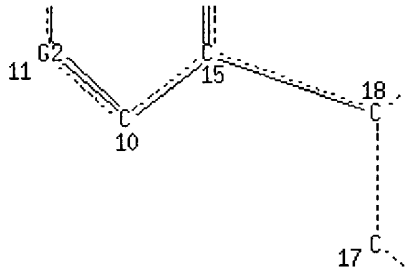

Page 2-A




Page 2-B




Page 3-A

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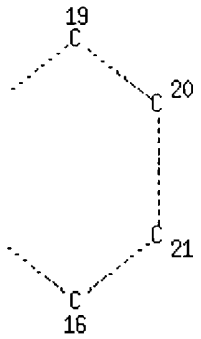


Page 3-C

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VAR G3=36/37
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VPA 8-12/13 S
NODE ATTRIBUTES:
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HCOUNT  IS M2     AT  32
HCOUNT  IS M1     AT  35
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NSPEC   IS R      AT   2
NSPEC   IS R      AT   3
NSPEC   IS R      AT   4
NSPEC   IS R      AT   5
NSPEC   IS R      AT   6
NSPEC   IS C      AT   7
NSPEC   IS C      AT   8
NSPEC   IS C      AT   9
NSPEC   IS R      AT  10
NSPEC   IS R      AT  11
NSPEC   IS R      AT  12
NSPEC   IS R      AT  13
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```
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NSPEC   IS R      AT  15
NSPEC   IS R      AT  16
NSPEC   IS R      AT  17
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NSPEC   IS R      AT  20
NSPEC   IS R      AT  21
NSPEC   IS C      AT  22
NSPEC   IS C      AT  23
NSPEC   IS C      AT  24
NSPEC   IS C      AT  25
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NSPEC   IS C      AT  27
NSPEC   IS C      AT  28
DEFAULT MLEVEL IS ATOM
MLEVEL  IS CLASS  AT   7  8 22 23 24 25 28 29 30 31 32 33 36 37
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS  37

STEREO ATTRIBUTES: NONE


=> s 16
SAMPLE SEARCH INITIATED 17:35:57 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -     10 TO ITERATE

100.0% PROCESSED      10 ITERATIONS                              6 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:           11 TO      389
PROJECTED ANSWERS:               6 TO      266

L7            6 SEA SSS SAM L6

=> s 16 full
THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 155.00 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 17:36:01 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -    290 TO ITERATE

100.0% PROCESSED     290 ITERATIONS                            188 ANSWERS
SEARCH TIME: 00.00.01

L8          188 SEA SSS FUL L6

=> file hcaplus
COST IN U.S. DOLLARS                              SINCE FILE      TOTAL
                                                     ENTRY    SESSION
FULL ESTIMATED COST                                 158.36     326.57

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)        SINCE FILE      TOTAL
                                                     ENTRY    SESSION
CA SUBSCRIBER PRICE                                   0.00      -0.69
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FILE 'HCAPLUS' ENTERED AT 17:36:04 ON 06 JUN 2004
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FILE COVERS 1907 - 6 Jun 2004  VOL 140 ISS 24
FILE LAST UPDATED: 4 Jun 2004  (20040604/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


=> d his

     (FILE 'HOME' ENTERED AT 17:22:43 ON 06 JUN 2004)

     FILE 'REGISTRY' ENTERED AT 17:23:01 ON 06 JUN 2004
L1              STRUCTURE UPLOADED
L2            6 S L1
L3          188 S L1 FULL

     FILE 'HCAPLUS' ENTERED AT 17:30:46 ON 06 JUN 2004
L4            1 S L3

     FILE 'CAOLD' ENTERED AT 17:31:21 ON 06 JUN 2004
L5            0 S L3

     FILE 'REGISTRY' ENTERED AT 17:31:26 ON 06 JUN 2004
L6              STRUCTURE UPLOADED
L7            6 S L6
L8          188 S L6 FULL

     FILE 'HCAPLUS' ENTERED AT 17:36:04 ON 06 JUN 2004

=> s l8/thu
              1 L8
         597239 THU/RL
L9            1 L8/THU
                  (L8 (L) THU/RL)

=> s l9 not l3
              1 L3
L10           0 L9 NOT L3

=> d l9, ibib abs fhitstr, 1

L9   ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2004 ACS on STN
```

Full Text | Citing References

ACCESSION NUMBER: 2004:182533 HCAPLUS
DOCUMENT NUMBER: 140:235608
TITLE: Preparation of 2-(biarylalkyl)amino-3-(cyanoalkanoylamino)pyridines as bradykinin B1 antagonists for treating pain and inflammation
INVENTOR(S): Kuduk, Scott D.; Bock, Mark G.; Feng, Dong-mei; Su, Dai-shi; Wai, Jenny Miu-chun
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 28 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2004044041 | A1 | 20040304 | US 2003-634426 | 20030805 |

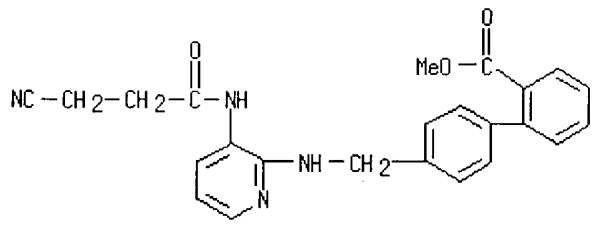
PRIORITY APPLN. INFO.: US 2002-401386P P 20020806
OTHER SOURCE(S): MARPAT 140:235608
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compds. [I; m = 1-4; X, Y = CH, or one is CH and the other is N; R1, R2 = H, alkyl; R3 = H, alkyl, haloalkyl, etc.; R4 = H, NO2, halo, etc.; R51, R52 = H, Me; or R51 and R52 together complete cycloalkyl ring; R61 = (un)substituted alkyl, cycloalkyl, alkenyl, etc.; R62, R63 = H, R61; with the proviso that not more than one of R61, R62 and R63 = heterocycle; R7 = H, alkyl, cycloalkyl, aryl, arylalkyl] which are bradykinin B1 antagonist compds. useful in the treatment or prevention of symptoms such as pain and inflammation assocd. with the bradykinin B1 pathway, were prepd. and formulated. E.g., a multi-step synthesis of II (starting from 4'-methyl-2-biphenylcarboxylic acid), was given. The compds. I have affinity for B1 receptor with IC50 values of < 5 μM.

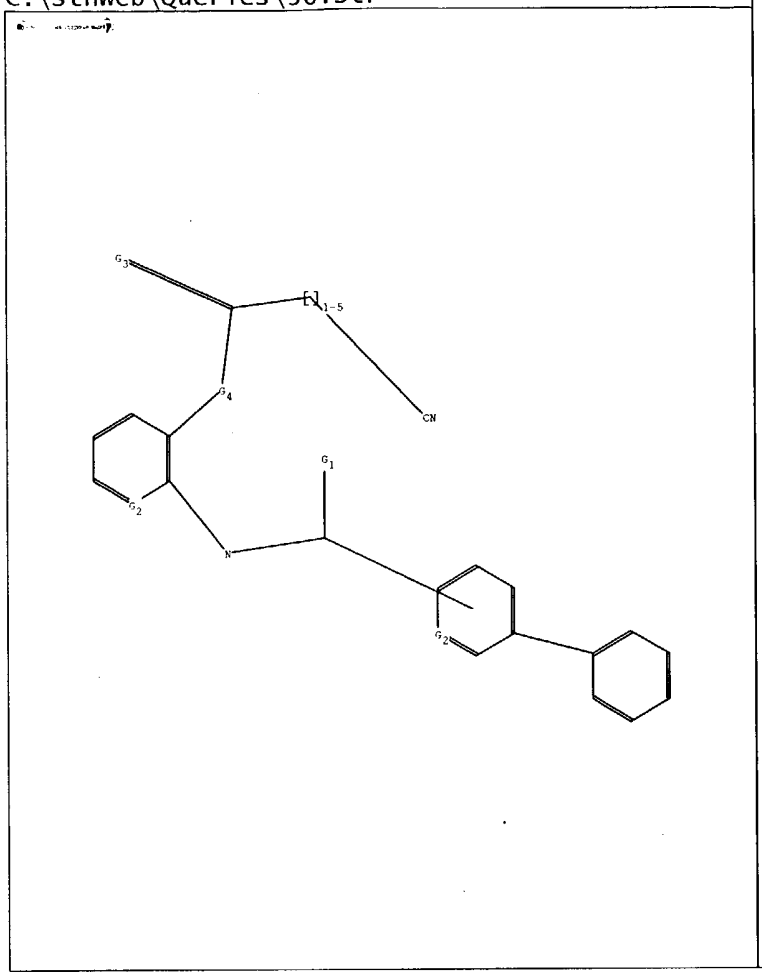
IT **668472-10-4P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 2-(biarylalkyl)amino-3-(cyanoalkanoylamino)pyridines as bradykinin B1 antagonists)

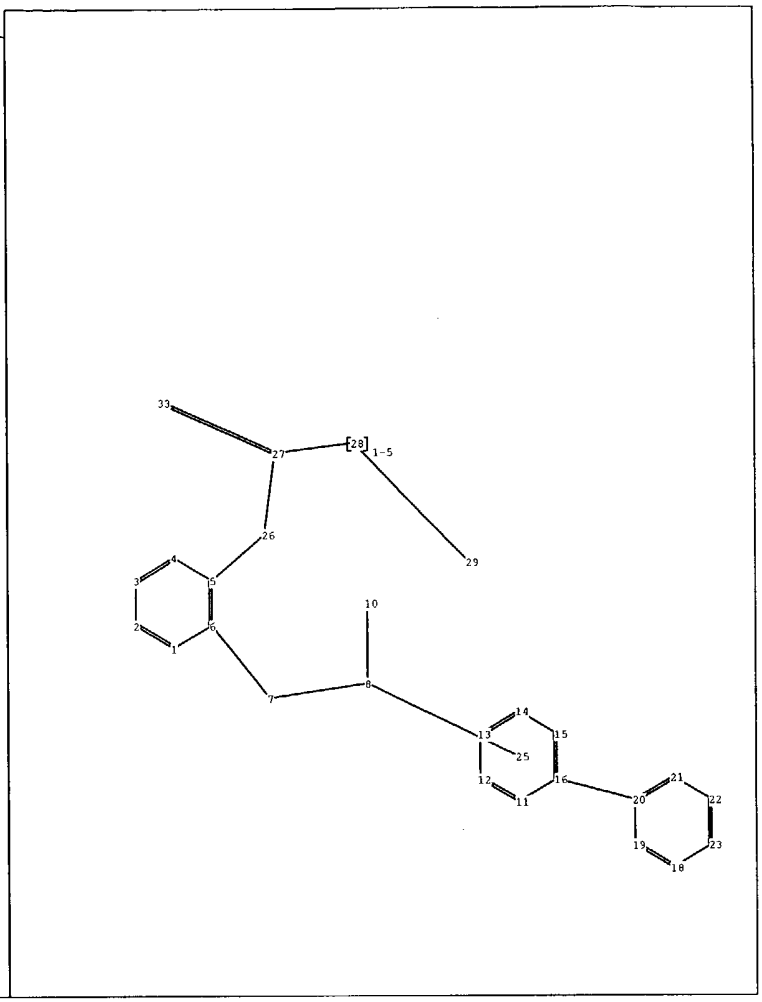
RN 668472-10-4 HCAPLUS
CN [1,1'-Biphenyl]-2-carboxylic acid, 4'-[[[3-[(3-cyano-1-oxopropyl)amino]-2-pyridinyl]amino]methyl]-, methyl ester (9CI) (CA INDEX NAME)




=>

C:\stnweb\Queries\56.str




chain nodes :
7 8 10 26 27 28 29 33
ring nodes :
1 2 3 4 5 6 11 12 13 14 15 16 18 19 20 21 22 23
chain bonds :
5-26 6-7 7-8 8-10 16-20 26-27 27-28 27-33 28-29
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 11-12 11-16 12-13 13-14 14-15 15-16 18-19 18-23
19-20 20-21 21-22 22-23
exact/norm bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-26 6-7 7-8 8-10 11-12 11-16 12-13 13-14 14-15
15-16 16-20 26-27 27-28 27-33 28-29
normalized bonds :
18-19 18-23 19-20 20-21 21-22 22-23
isolated ring systems :
containing 1 : 11 : 18 :

G1:H,Ak,OH,NH2,F

G2:N,CH

G3:O,S

G4:O,N

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:CLASS 10:CLASS 11:Atom
12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 18:Atom 19:Atom 20:Atom 21:Atom 22:Atom
23:Atom 25:CLASS 26:CLASS 27:CLASS 28:CLASS 29:CLASS 33:CLASS

```
* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

NEWS  1            Web Page URLs for STN Seminar Schedule - N. America
NEWS  2            "Ask CAS" for self-help around the clock
NEWS  3  JAN 27    Source of Registration (SR) information in REGISTRY updated
                   and searchable
NEWS  4  JAN 27    A new search aid, the Company Name Thesaurus, available in
                   CA/CAplus
NEWS  5  FEB 05    German (DE) application and patent publication number format
                   changes
NEWS  6  MAR 03    MEDLINE and LMEDLINE reloaded
NEWS  7  MAR 03    MEDLINE file segment of TOXCENTER reloaded
NEWS  8  MAR 03    FRANCEPAT now available on STN
NEWS  9  MAR 29    Pharmaceutical Substances (PS) now available on STN
NEWS 10  MAR 29    WPIFV now available on STN
NEWS 11  MAR 29    New monthly current-awareness alert (SDI) frequency in RAPRA
NEWS 12  APR 26    PROMT: New display field available
NEWS 13  APR 26    IFIPAT/IFIUDB/IFICDB: New super search and display field
                   available
NEWS 14  APR 26    LITALERT now available on STN
NEWS 15  APR 27    NLDB: New search and display fields available
NEWS 16  May 10    PROUSDDR now available on STN
NEWS 17  May 19    PROUSDDR: One FREE connect hour, per account, in both May
                   and June 2004
NEWS 18  May 12    EXTEND option available in structure searching
NEWS 19  May 12    Polymer links for the POLYLINK command completed in REGISTRY
NEWS 20  May 17    FRFULL now available on STN
NEWS 21  May 27    STN User Update to be held June 7 and June 8 at the SLA 2004
                   Conference
NEWS 22  May 27    New UPM (Update Code Maximum) field for more efficient patent
                   SDIs in CAplus
NEWS 23  May 27    CAplus super roles and document types searchable in REGISTRY
NEWS 24  May 27    Explore APOLLIT with free connect time in June 2004

NEWS EXPRESS  MARCH 31 CURRENT WINDOWS VERSION IS V7.00A, CURRENT
              MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
              AND CURRENT DISCOVER FILE IS DATED 26 APRIL 2004
NEWS HOURS    STN Operating Hours Plus Help Desk Availability
NEWS INTER    General Internet Information
NEWS LOGIN    Welcome Banner and News Items
NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
NEWS WWW      CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
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  * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 18:28:29 ON 06 JUN 2004

=> file reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                      ENTRY     SESSION
FULL ESTIMATED COST                                    0.21        0.21
```

FILE 'REGISTRY' ENTERED AT 18:28:56 ON 06 JUN 2004
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES: 4 JUN 2004 HIGHEST RN 689739-78-4
DICTIONARY FILE UPDATES: 4 JUN 2004 HIGHEST RN 689739-78-4

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> file hcaplus

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 0.42 | 0.63 |

FILE 'HCAPLUS' ENTERED AT 18:29:24 ON 06 JUN 2004
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FILE COVERS 1907 - 6 Jun 2004 VOL 140 ISS 24
FILE LAST UPDATED: 4 Jun 2004 (20040604/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> s bradykinin and pain?
16399 BRADYKININ
191 BRADYKININS
16426 BRADYKININ
(BRADYKININ OR BRADYKININS)
119947 PAIN?
L1 908 BRADYKININ AND PAIN?

```
=> s bradykinin () ?agonist
         16399 BRADYKININ
           191 BRADYKININS
         16426 BRADYKININ
                 (BRADYKININ OR BRADYKININS)
        202089 ?AGONIST
L2         535 BRADYKININ (W) ?AGONIST

=> s l2 and pain
         33270 PAIN
           848 PAINS
         33878 PAIN
                 (PAIN OR PAINS)
L3          47 L2 AND PAIN

=> s l3 and dt/review
'REVIEW' IS NOT A VALID FIELD CODE
             0 DT/REVIEW
L4           0 L3 AND DT/REVIEW

=> s l3 and review/dt
       1732111 REVIEW/DT
L5           6 L3 AND REVIEW/DT

=> d l5, ibib abs hitstr, 1-6

L5   ANSWER 1 OF 6  HCAPLUS  COPYRIGHT 2004 ACS on STN
```

Full Text | Citing References

ACCESSION NUMBER: 2002:148931 HCAPLUS
DOCUMENT NUMBER: 136:145353
TITLE: **Bradykinin antagonist**: current status and perspective
AUTHOR(S): Hirayama, Yoshitaka; Kayakiri, Hiroshi
CORPORATE SOURCE: Medicinal Biology Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., Yodogawa-ku, Osaka, 532-8514, Japan
SOURCE: Nippon Yakurigaku Zasshi (2002), 119(1), 45-53
CODEN: NYKZAU; ISSN: 0015-5691
PUBLISHER: Nippon Yakuri Gakkai
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Japanese

AB A review. The kallikrein-kinin system plays an important role in many physiol. and pathophysiol. conditions such as homeostasis of circulation, inflammation/allergy, **pain**, shock, etc. Two types of kinin receptor are known, bradykinin (BK) B1 receptor and BK B2 receptor. B2 receptors are constitutively expressed and mediate most physiol. actions of kinins, whereas B1 receptors are highly inducible upon inflammatory stimulation or tissue injury, suggesting that they are involved in inflammation and/or nociception. Only three peptide type B2 antagonists, NPC 567, CP-0127, and HOE-140, have been evaluated in clin. studies so far, and some beneficial effects of B2 antagonists have been shown for rhinitis, asthma, systemic inflammatory response syndrome/sepsis, and brain injury. However, the results were less convincing than expected. Now several potent and orally active nonpeptide B2-receptor antagonists have been found, which are expected to overcome the weak point of the peptide type antagonists and clarify the therapeutic potential of the B2-receptor antagonist for novel indications as well as those mentioned above. As for B1 receptors, no antagonist has been tested in a clin. trial. The important role of B1 receptors is just being elucidated by use of peptide type antagonists or B1 receptor gene knockout mice. The further

development of newer B1 antagonists and clin. evaluation is desired.

L5 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:298214 HCAPLUS
DOCUMENT NUMBER: 134:294182
TITLE: Inflammation-allergy and prostanoids. (1) Prostanoids in experimental inflammatory reaction
AUTHOR(S): Ueno, Akinori; Ohishi, Sachiko
CORPORATE SOURCE: Dep. Pharmacol., Sch. Pharm. Sci., Kitasato Univ., 5-9-1 Shirokane, Minato-ku, Tokyo, 108-8642, Japan
SOURCE: Nippon Yakurigaku Zasshi (2001), 117(4), 255-261
CODEN: NYKZAU; ISSN: 0015-5691
PUBLISHER: Nippon Yakuri Gakkai
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Japanese

AB A review with 22 refs. It is known that prostaglandins (PGs) modify the inflammatory reaction in concert with other biol. active mediators. However, characteristics of these interactions or modulating actions have not yet been clarified well. Recently, the prodn. of mice with specific receptor deficiencies by using the gene targeting procedure for PG receptors has accelerated elucidation of the roles of PGs through correlation of their phenotypes and exptl. features. Here I discuss roles of PGs in exptl. paw edema, the writhing reaction of a **pain** model, and regulation of cytokine formation, as detd. using some PG-receptor-deficient mice. From the expt. of carrageenin-induced paw edema in IP receptor-deficient mice, with an indomethacin or **bradykinin antagonist**, we conclude that bradykinin initially induces paw swelling and then stimulates the release PGI2, which in turn enhances the swelling with bradykinin. By comparing the writhing responses in IP-deficient and wild-type mice, we found that PGI2 is a main mediator for this **pain** reaction. However, in the LPS-pretreated mice, not only PGI2 but also other PGs produced by COX-2 may be involved in **pain** induction. Formation of TNFα and IL-10 was modified with PGI2 or PGE2; the formation of TNFα was down-regulated by the stimulation via IP-, EP2- or EP4 receptor, but that of IL-10 was up-regulated by these receptors, resulting in an anti-inflammatory effect.

L5 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2000:584130 HCAPLUS
DOCUMENT NUMBER: 133:246693
TITLE: Bradykinin antagonists: new opportunities
AUTHOR(S): Bock, Mark G.; Longmore, Jeanette
CORPORATE SOURCE: Merck Research Laboratories, West Point, PA, 19486, USA
SOURCE: Current Opinion in Chemical Biology (2000), 4(4), 401-406
CODEN: COCBF4; ISSN: 1367-5931
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

QD550. C87

AB A review with 40 refs. The pro-inflammatory, **pain** producing, and cardiovascular effects of bradykinin B2 receptor activation are well characterized. Bradykinin B1 receptors also produce inflammation and **pain**. Therefore, antagonists are expected to be anti-inflammatory/analgesic drugs. Other exploitable clin. opportunities may exist. The newly discovered non-peptide B2 receptor antagonists and the

equiv. B1 receptor pharmacol. agents, which are in the pipeline, are suitable preclin. tools to properly evaluate potential utilities.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN
Full Text | Citing References

ACCESSION NUMBER: 1997:492671 HCAPLUS
DOCUMENT NUMBER: 127:170901
TITLE: Nonconventional analgesics: bradykinin antagonists
AUTHOR(S): Elguero, Jose; Rozas, Isabel
CORPORATE SOURCE: Instituto de Quimica Medica (C. S. I. C.), Spain
SOURCE: Anales de la Real Academia de Farmacia (1997), 63(1), 173-190
CODEN: ARAFAY; ISSN: 0034-0618
PUBLISHER: Real Academia de Farmacia
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Spanish
AB A review with 34 refs. Bradykinin and kallidin, "kinins", are generated by the activity of kallikreins (proteolytic enzymes) on kininogens. Kinins elicit pathophysiol. responses including **pain** and hyperalgesia. Kinins receptors are classified according to the relative potencies of agonist and antagonists. Regoli and Barabe proposed two subtypes of receptors, B1 and B2. Hundreds of agonists analogs of bradykinin were prepd. before the first antagonist compds. appeared. Synthetic efforts have been oriented towards peptidic analogs until few years ago when the search of non-peptidic antagonists started. The distribution of receptor B1 in the human being is very limited and probably this subtype plays an unimportant role on human diseases. Two generation of peptidic antagonists of the B2 receptor have been developed. The second generation has compds. two orders of magnitude more potent as analgesics than the first generation ones and the most important deriv. was icatibant. The first non-peptidic antagonist of the B2 receptor, described in 1993, has two phosphonium cations sepd. by a modified amino acid. Many derivs. of this dication have been prepd. Another non-peptidic compd. antagonist of B2 is the natural product Martinelline. Mol. modeling and QSAR studies have been carried out on bradykinin as well as on its antagonists.

L5 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN
Full Text | Citing References

ACCESSION NUMBER: 1993:401036 HCAPLUS
DOCUMENT NUMBER: 119:1036
TITLE: Therapeutic prospects of bradykinin receptor antagonists
AUTHOR(S): Sharma, J. N.
CORPORATE SOURCE: Sch. Med. Sci., Univ. Sains Malaysia, Kubang Kerian, 16150, Malay.
SOURCE: General Pharmacology (1993), 24(2), 267-74
CODEN: GEPHDP; ISSN: 0306-3623
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 77 refs. Bradykinin (BK) and related kinins may act on 4 types of receptors designated as B1, B2, B3, and B4. It seems that the B2 receptors are most commonly found in various vascular and non-vascular smooth muscles, whereas B1 receptors are formed in vitro during trauma, and injury, and are found in bone tissues. These BK receptors are involved in the regulations of various physiol. and pathol. processes. The mode of kinin actions are based upon the interactions between the

kinin and their specific receptors, which can led to activation of several second-messenger systems. Numerous BK receptor antagonists have been synthesized with prime aim to treat diseases caused by excessive kinin prodn. These diseases are RA, inflammatory diseases of the bowel, asthma, rhinitis and sore throat, allergic reactions, **pain**, inflammatory skin disorders, endotoxin and anaphylactic shock and coronary heart diseases. On the other hand, BK receptor antagonists could be contraindicated in hypertension, since these drugs may antagonize the antihypertensive therapy and/or may trigger the hypertensive crisis. It is worth suggesting that the BK receptor agonists might be useful antihypertensive drugs.

L5 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1991:421390 HCAPLUS
DOCUMENT NUMBER: 115:21390
TITLE: Bradykinin antagonists in **pain** and inflammation
AUTHOR(S): Steranka, Larry R.; Burch, Ronald M.
CORPORATE SOURCE: Nova Pharm. Corp., Baltimore, MD, USA
SOURCE: Inflammatory Disease and Therapy (1990), 5(Bradykinin Antagonists), 191-211
CODEN: IDITE8; ISSN: 1047-5028
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 74 refs. discussing the effects of peptide bradykinin antagonists and certain kallikrein inhibitors on models of inflammation and **pain**.

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=> d his

     (FILE 'HOME' ENTERED AT 18:28:29 ON 06 JUN 2004)

     FILE 'REGISTRY' ENTERED AT 18:28:56 ON 06 JUN 2004

     FILE 'HCAPLUS' ENTERED AT 18:29:24 ON 06 JUN 2004
L1           908 S BRADYKININ AND PAIN?
L2           535 S BRADYKININ () ?AGONIST
L3            47 S L2 AND PAIN
L4             0 S L3 AND DT/REVIEW
L5             6 S L3 AND REVIEW/DT

=> s l2 and inflamm?
         182244 INFLAMM?
L6          117 L2 AND INFLAMM?

=> s l6 and review/dt
        1732111 REVIEW/DT
L7           14 L6 AND REVIEW/DT

=> d his

     (FILE 'HOME' ENTERED AT 18:28:29 ON 06 JUN 2004)

     FILE 'REGISTRY' ENTERED AT 18:28:56 ON 06 JUN 2004

     FILE 'HCAPLUS' ENTERED AT 18:29:24 ON 06 JUN 2004
L1           908 S BRADYKININ AND PAIN?
L2           535 S BRADYKININ () ?AGONIST
```

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L3            47 S L2 AND PAIN
L4             0 S L3 AND DT/REVIEW
L5             6 S L3 AND REVIEW/DT
L6           117 S L2 AND INFLAMM?
L7            14 S L6 AND REVIEW/DT

=> s l7 and l5
L8             5 L7 AND L5

=> d l8, ibib abs, 1-5

L8   ANSWER 1 OF 5  HCAPLUS  COPYRIGHT 2004 ACS on STN
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Full Text | Citing References

```
ACCESSION NUMBER:         2002:148931  HCAPLUS
DOCUMENT NUMBER:          136:145353
TITLE:                    Bradykinin antagonist: current status and perspective
AUTHOR(S):                Hirayama, Yoshitaka; Kayakiri, Hiroshi
CORPORATE SOURCE:         Medicinal Biology Research Laboratories, Fujisawa
                          Pharmaceutical Co., Ltd., Yodogawa-ku, Osaka,
                          532-8514, Japan
SOURCE:                   Nippon Yakurigaku Zasshi (2002), 119(1), 45-53
                          CODEN: NYKZAU; ISSN: 0015-5691
PUBLISHER:                Nippon Yakuri Gakkai
DOCUMENT TYPE:            Journal; General Review
LANGUAGE:                 Japanese
AB   A review.  The kallikrein-kinin system plays an important role in many
     physiol. and pathophysiol. conditions such as homeostasis of circulation,
     inflammation/allergy, pain, shock, etc.  Two types of kinin receptor
     are known, bradykinin (BK) B1 receptor and BK B2 receptor.  B2 receptors
     are constitutively expressed and mediate most physiol. actions of kinins,
     whereas B1 receptors are highly inducible upon inflammatory stimulation
     or tissue injury, suggesting that they are involved in inflammation
     and/or nociception.  Only three peptide type B2 antagonists, NPC 567,
     CP-0127, and HOE-140, have been evaluated in clin. studies so far, and
     some beneficial effects of B2 antagonists have been shown for rhinitis,
     asthma, systemic inflammatory response syndrome/sepsis, and brain
     injury.  However, the results were less convincing than expected.  Now
     several potent and orally active nonpeptide B2-receptor antagonists have
     been found, which are expected to overcome the weak point of the peptide
     type antagonists and clarify the therapeutic potential of the B2-receptor
     antagonist for novel indications as well as those mentioned above.  As for
     B1 receptors, no antagonist has been tested in a clin. trial.  The
     important role of B1 receptors is just being elucidated by use of peptide
     type antagonists or B1 receptor gene knockout mice.  The further
     development of newer B1 antagonists and clin. evaluation is desired.

L8   ANSWER 2 OF 5  HCAPLUS  COPYRIGHT 2004 ACS on STN
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Full Text | Citing References

```
ACCESSION NUMBER:         2001:298214  HCAPLUS
DOCUMENT NUMBER:          134:294182
TITLE:                    Inflammation-allergy and prostanoids. (1)
                          Prostanoids in experimental inflammatory reaction
AUTHOR(S):                Ueno, Akinori; Ohishi, Sachiko
CORPORATE SOURCE:         Dep. Pharmacol., Sch. Pharm. Sci., Kitasato Univ.,
                          5-9-1 Shirokane, Minato-ku, Tokyo, 108-8642, Japan
SOURCE:                   Nippon Yakurigaku Zasshi (2001), 117(4), 255-261
                          CODEN: NYKZAU; ISSN: 0015-5691
PUBLISHER:                Nippon Yakuri Gakkai
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DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Japanese
AB A review with 22 refs. It is known that prostaglandins (PGs) modify the **inflammatory** reaction in concert with other biol. active mediators. However, characteristics of these interactions or modulating actions have not yet been clarified well. Recently, the prodn. of mice with specific receptor deficiencies by using the gene targeting procedure for PG receptors has accelerated elucidation of the roles of PGs through correlation of their phenotypes and exptl. features. Here I discuss roles of PGs in exptl. paw edema, the writhing reaction of a **pain** model, and regulation of cytokine formation, as detd. using some PG-receptor-deficient mice. From the expt. of carrageenin-induced paw edema in IP receptor-deficient mice, with an indomethacin or **bradykinin antagonist**, we conclude that bradykinin initially induces paw swelling and then stimulates the release PGI2, which in turn enhances the swelling with bradykinin. By comparing the writhing responses in IP-deficient and wild-type mice, we found that PGI2 is a main mediator for this **pain** reaction. However, in the LPS-pretreated mice, not only PGI2 but also other PGs produced by COX-2 may be involved in **pain** induction. Formation of TNFα and IL-10 was modified with PGI2 or PGE2; the formation of TNFα was down-regulated by the stimulation via IP-, EP2- or EP4 receptor, but that of IL-10 was up-regulated by these receptors, resulting in an anti-**inflammatory** effect.

L8 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
Full Text | Citing References
ACCESSION NUMBER: 2000:584130 HCAPLUS
DOCUMENT NUMBER: 133:246693
TITLE: Bradykinin antagonists: new opportunities
AUTHOR(S): Bock, Mark G.; Longmore, Jeanette
CORPORATE SOURCE: Merck Research Laboratories, West Point, PA, 19486, USA
SOURCE: Current Opinion in Chemical Biology (2000), 4(4), 401-406
CODEN: COCBF4; ISSN: 1367-5931
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 40 refs. The pro-**inflammatory**, **pain** producing, and cardiovascular effects of bradykinin B2 receptor activation are well characterized. Bradykinin B1 receptors also produce **inflammation** and **pain**. Therefore, antagonists are expected to be anti-**inflammatory**/analgesic drugs. Other exploitable clin. opportunities may exist. The newly discovered non-peptide B2 receptor antagonists and the equiv. B1 receptor pharmacol. agents, which are in the pipeline, are suitable preclin. tools to properly evaluate potential utilities.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

QP 550 .C87

L8 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
Full Text | Citing References
ACCESSION NUMBER: 1993:401036 HCAPLUS
DOCUMENT NUMBER: 119:1036
TITLE: Therapeutic prospects of bradykinin receptor antagonists
AUTHOR(S): Sharma, J. N.
CORPORATE SOURCE: Sch. Med. Sci., Univ. Sains Malaysia, Kubang Kerian, 16150, Malay.

SOURCE: General Pharmacology (1993), 24(2), 267-74
CODEN: GEPHDP; ISSN: 0306-3623
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

e journal = AOMIS

AB A review with 77 refs. Bradykinin (BK) and related kinins may act on 4 types of receptors designated as B1, B2, B3, and B4. It seems that the B2 receptors are most commonly found in various vascular and non-vascular smooth muscles, whereas B1 receptors are formed in vitro during trauma, and injury, and are found in bone tissues. These BK receptors are involved in the regulations of various physiol. and pathol. processes. The mode of kinin actions are based upon the interactions between the kinin and their specific receptors, which can led to activation of several second-messenger systems. Numerous BK receptor antagonists have been synthesized with prime aim to treat diseases caused by excessive kinin prodn. These diseases are RA, **inflammatory** diseases of the bowel, asthma, rhinitis and sore throat, allergic reactions, **pain**, **inflammatory** skin disorders, endotoxin and anaphylactic shock and coronary heart diseases. On the other hand, BK receptor antagonists could be contraindicated in hypertension, since these drugs may antagonize the antihypertensive therapy and/or may trigger the hypertensive crisis. It is worth suggesting that the BK receptor agonists might be useful antihypertensive drugs.

L8 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1991:421390 HCAPLUS
DOCUMENT NUMBER: 115:21390
TITLE: Bradykinin antagonists in **pain** and **inflammation**
AUTHOR(S): Steranka, Larry R.; Burch, Ronald M.
CORPORATE SOURCE: Nova Pharm. Corp., Baltimore, MD, USA
SOURCE: Inflammatory Disease and Therapy (1990), 5(Bradykinin Antagonists), 191-211
CODEN: IDITE8; ISSN: 1047-5028
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 74 refs. discussing the effects of peptide bradykinin antagonists and certain kallikrein inhibitors on models of **inflammation** and **pain**.

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     (FILE 'HOME' ENTERED AT 18:28:29 ON 06 JUN 2004)

     FILE 'REGISTRY' ENTERED AT 18:28:56 ON 06 JUN 2004

     FILE 'HCAPLUS' ENTERED AT 18:29:24 ON 06 JUN 2004
L1           908 S BRADYKININ AND PAIN?
L2           535 S BRADYKININ () ?AGONIST
L3            47 S L2 AND PAIN
L4             0 S L3 AND DT/REVIEW
L5             6 S L3 AND REVIEW/DT
L6           117 S L2 AND INFLAMM?
L7            14 S L6 AND REVIEW/DT
L8             5 S L7 AND L5

=> s l2 and osteoarthrit?
          5656 OSTEOARTHRIT?
L9           3 L2 AND OSTEOARTHRIT?
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=> s l9 and review/dt
       1732111 REVIEW/DT
L10           0 L9 AND REVIEW/DT

=> d l9, ibib abs, 1-3

L9   ANSWER 1 OF 3  HCAPLUS  COPYRIGHT 2004 ACS on STN
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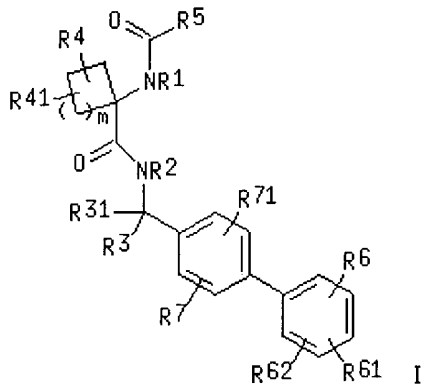
Full Text | Citing References

ACCESSION NUMBER: 2003:633647 HCAPLUS
DOCUMENT NUMBER: 139:179895
TITLE: Preparation of N-biphenylmethyl cycloalkanecarboxamides as bradykinin antagonists for treatment of conditions associated with the bradykinin B1 pathway.
INVENTOR(S): Wood, Michael R.; Anthony, Neville J.; Bock, Mark G.; Feng, Dong-Mei; Kuduk, Scott D.; Su, Dai-Shi; Wai, Jenny Miu-Chun
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 89 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003066577 | A1 | 20030814 | WO 2003-US3338 | 20030204 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2003220375 | A1 | 20031127 | US 2003-354674 | 20030130 |

PRIORITY APPLN. INFO.: US 2002-355062P P 20020208
US 2002-410172P P 20020912

OTHER SOURCE(S): MARPAT 139:179895
GI




I

AB Title compds. [I; R1, R2 = H, alkyl; R3 = H, alkyl, haloalkyl; R31 = alkyl, haloalkyl; R4, R41 = H, halo, (substituted) alkyl; R4R41 = atoms to form (substituted) methylene; R5 = alkynyl, (substituted) alkyl, alkenyl, cycloalkyl, ar(alkyl), heterocyclyl(alkyl), etc.; R6 = cycloalkyl, halo, cyano, NO2, (substituted) alkyl, alkenyl, amino, acylamino, heterocyclyl, acyl, etc.; R61, R62 = H, R6; R7, R71 = H, halo, cyano, NO2, alkyl, haloalkyl, amino, CO2H, etc.; m = 0, 1], were prepd. for treatment of pain and inflammation (no data). Thus, tert-Bu (1R)-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethylcarbamate (prepn. given), Me 2-fluoro-6-iodobenzoate, K2CO3, tri-o-tolylphosphine, and palladium acetate were heated at 90° for 18 h in THF/H2O to provide Me 4'-[(1R)-1-[(tert-butoxycarbonyl)amino]ethyl]-3-fluoro-1,1'-biphenylcarboxylate. This was treated with HCl in MeOH to give an amine hydrochloride. The above amine hydrochloride along with 1-[(tert-butoxycarbonyl)amino]cyclopropanecarboxylic acid, HOBt.H2O, triethylamine, and EDCI were stirred 16.5 h in THF to give 86% Me 4'-[(1R)-1-[[[1-[(tert-butoxycarbonyl)amino]cyclopropyl]carbonyl]amino]ethyl]-3-fluoro-1,1'-bibiphenyl-2-carboxylate. This was stirred with HCl in MeOH to give a solid amine hydrochloride. The above amine hydrochloride, trifluoropropionic acid, HOBt.H2O, triethylamine, and EDCI in THF/DMF were stirred 18 h to give 67% Me 3-fluoro-4'-[(1R)-1-[[[1-[(3,3,3-trifluoropropanoyl)amino]cyclopropyl]carbonyl]amino]ethyl]-1,1'-bibiphenyl-2-carboxylate.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

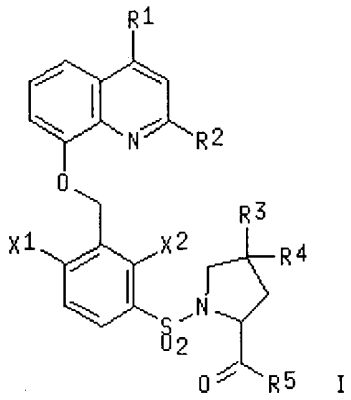
L9 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:470490 HCAPLUS
DOCUMENT NUMBER: 139:53305
TITLE: Preparation of N-benzenesulfonyl-L-proline compounds as bradykinin antagonists
INVENTOR(S): Nukui, Seiji; Koike, Hiroki; Kawai, Makoto; Katsu, Yasuhiro
PATENT ASSIGNEE(S): Pfizer Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 17 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| JP 2003171377 | A2 | 20030620 | JP 2001-371081 | 20011205 |

PRIORITY APPLN. INFO.: JP 2001-371081 20011205
OTHER SOURCE(S): MARPAT 139:53305
GI



I

AB The title compds. (I) or pharmacol. acceptable salts thereof [X1, X2 = halo, C1-4 alkyl; R1, R2 = H, C1-4 alkyl; R3, R4 = H, halo; R5 = (a) C3-9 diazacycloalkyl optionally substituted C5-11 azabicycloalkyl, (b) C5-11 azabicycloalkyl optionally substituted by C3-9 azacycloalkyl-NH-(C1-4 alkyl), (c) -NH-C1-3 alkyl-CO-C5-11 diazabicycloalkyl, (d) -NH-C1-3 alkyl-CONH-C5-11 azabicycloalkyl where C5-11 azabicycloalkyl is optionally substituted by C1-4 alkyl, (e) C3-9 azacycloalkyl optionally substituted by C3-9 azacycloalkyl, (f) -NH-C1-5 alkyl-NHCO-C4-9 cycloalkyl-NH2] are prepd. These compds. are useful for the treatment of diseases mediated by bradykinin such as inflammation, chronic articular rheumatism, cystitis, brain edema after trauma, hemorrhage, or surgery, brain edema (general), liver cirrhosis, Alzheimer's disease, cardiovascular diseases, pain, cold, allergy, asthma, pancreatitis, burn, viral infection, head trauma, multiple trauma, rhinitis, liver-kidney failure, diabetes, metastasis, neovascularization, corneal opacity, glaucoma, ocular pain, high ocular pressure, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, multiple sclerosis, stroke, cytotoxic brain edema, brain edema related to metabolic disease, **osteoarthritis** (arthrosis deformans), migraine, neuropathic pain, itching, brain tumor, pseudo-brain tumor, hydrocephalus, spinal cord injury, spinal cord dropsy, neurodegenerative disease, respiratory disease, diuresis, increase in the excretion of sodium and potassium, chronic obstructive pulmonary disease, brain damage after trauma, and septicemia. Thus, (3S)-3-(1-piperazinyl)-1-azabicyclo[2.2.2]octane was condensed with N-[2,4-dichloro-3-(2,4-dimethylquinolin-8-yloxymethyl)phenylsulfonyl]-L-proline using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride and 1-hydroxybenzotriazole in CH2Cl2 at room temp. overnight to give 8-[[3-[[(2S)-2-[[4-[(3S)-1-azabicyclo[2.2.2]octan-3-yl]-1-piperazinyl]carbonyl]-1-pyrrolidinyl]sulfonyl]-2,6-dichlorobenzyl]oxy]-2,4-dimethylquinoline. The compds. I showed IC50 of 0.1-4 nM for inhibiting the binding of [3H]bradykinin to CHO-K1 cell membrane prepd. from monkey ileum.

L9 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:446120 HCAPLUS
DOCUMENT NUMBER: 137:33534

TITLE: Preparation of N-benzenesulfonyl-L-proline compounds as bradykinin antagonists

INVENTOR(S): Katsu, Yasuhiro; Kawai, Makoto; Koike, Hiroki; Nukui, Seiji

PATENT ASSIGNEE(S): Pfizer Inc., USA

SOURCE: Eur. Pat. Appl., 19 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

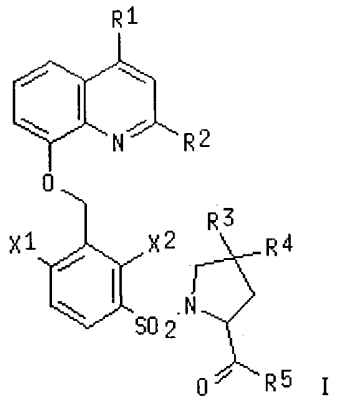
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 1213289 | A1 | 20020612 | EP 2001-310151 | 20011204 |
| EP 1213289 | B1 | 20031105 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| BR 2001005775 | A | 20020813 | BR 2001-5775 | 20011204 |
| AT 253575 | E | 20031115 | AT 2001-310151 | 20011204 |
| PT 1213289 | T | 20040130 | PT 2001-310151 | 20011204 |
| JP 2002220387 | A2 | 20020809 | JP 2001-371430 | 20011205 |
| US 2002128271 | A1 | 20020912 | US 2001-10863 | 20011205 |
| US 6734306 | B2 | 20040511 | | |

PRIORITY APPLN. INFO.: US 2000-251225P P 20001205

OTHER SOURCE(S): MARPAT 137:33534

GI



I

AB Proline derivs. I [X1, X2 = halo or C1-4 alkyl; R1, R2 = H or C1-4 alkyl; R3, R4 = H or halo; R5 = C3-9 diazacycloalkyl optionally substituted with C5-11 azabicycloalkyl, C3-9 azacycloalkyl-NH-(C5-11 azabicycloalkyl optionally substituted with C1-4 alkyl), NH-C1-3 alkyl-C(O)-C5-11 diazabicycloalkyl, NH-C1-3 alkyl-C(O)-NH-C5-11 azabicycloalkyl, the C5-11 azabicycloalkyl being optionally substituted with C1-4 alkyl, C3-9 azacycloalkyl optionally substituted with C3-9 azacycloalkyl, or NH-C1-5 alkyl-NHC(O)-C4-9 cycloalkyl-NH] or their pharmaceutically-acceptable salts were prepd. for the treatment of medical conditions mediated by bradykinin, e.g., inflammation, allergic rhinitis, and pain. Thus, 8-[[3-[[(2S)-2-[[4-[(3S)-1-azabicyclo[2.2.2]oct-3-yl]-1-piperazinyl]carbonyl]pyrrolidinyl]sulfonyl]-2,6-dichlorobenzyl]oxy]-2,4-dimethylquinoline hydrochloride was prepd. via acylation of 3(S)-(1-piperazinyl)-1-azabicyclo[2.2.2]octane (prepn. given). The biol. activity of compds. of the invention was detd. by their ability to inhibit the binding of bradykinin at its receptor sites in recombinant human

bradykinin B2 receptor expressing CHO-K1 cells (IC50 values for the synthesized compds. were 0.1-4 nM).
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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FILE 'REGISTRY' ENTERED AT 18:28:56 ON 06 JUN 2004

FILE 'HCAPLUS' ENTERED AT 18:29:24 ON 06 JUN 2004
L1 908 S BRADYKININ AND PAIN?
L2 535 S BRADYKININ () ?AGONIST
L3 47 S L2 AND PAIN
L4 0 S L3 AND DT/REVIEW
L5 6 S L3 AND REVIEW/DT
L6 117 S L2 AND INFLAMM?
L7 14 S L6 AND REVIEW/DT
L8 5 S L7 AND L5
L9 3 S L2 AND OSTEOARTHRIT?
L10 0 S L9 AND REVIEW/DT

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32678 ARTHRITIS?
L11 13 L2 AND ARTHRITIS?

=> s l11 and review/dt
1732111 REVIEW/DT
L12 1 L11 AND REVIEW/DT

=> d l12, ibib abs, 1

L12 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2004 ACS on STN
Full Text | Citing References
ACCESSION NUMBER: 1994:426082 HCAPLUS
DOCUMENT NUMBER: 121:26082
TITLE: New and highly potent bradykinin antagonists
AUTHOR(S): Knolle, J.; Wirth, K.; Breipohl, G.; Henke, S.; Schoelkens, B.
CORPORATE SOURCE: HOECHST AG, Frankfurt/Main, D-6230/80, Germany
SOURCE: Actualites de Chimie Therapeutique (1993), 20, 259-64
CODEN: ACHTD9; ISSN: 0338-8999
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 15 refs. Results obtained with HOE 140 underline its unique properties and suggest its use in the therapy of allergic conditions, asthma and **arthritis**.

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